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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,921	02/17/2004	Frank L. Meyskens JR.	UCIVN-058C	1912

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,921	MEYSKENS ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group IV, claims 84-87 in the reply filed on 10/2/2006 is acknowledged. However, upon further consideration, Examiner notes that applicants cancelled claims 21-99 in the Transmittal Letter dated 2/17/2004. As such, only claims 1-20 are currently pending.

The Restriction Requirement mailed 6/2/2006 is hereby **withdrawn** and pending claims 1-20 will be examined.

Status of the Claims

Claims 1-20 are currently pending and are the subject of this Office Action. Applicants cancelled claims 21-99 in the Transmittal Letter dated 2/17/2004. This is the first Office Action on the merits of the pending claims.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. § 120, 121, or 365(c) is acknowledged. This application claims priority to U.S. Provisional Application No. 60/227,714, filed August 24, 2000 and U.S. Non-Provisional Application No. 09/938,846, filed 8/24/2001.

Prior-filed Non-Provisional Application No. 09/938,846 became abandoned on 11/17/2003. The filing date of the instant application is 2/17/2004. As such, the '846 application was not co-pending with the present application. A review of the '846 application

reveals a Non-Final Office Action was mailed on 8/14/2003. No response or extension of time was filed in the '846 case after the mailing of the Non-Final Office Action. As a result, the application became abandoned after the 3-month time period for reply (11/17/2003).

The abandonment of the '846 application on 11/17/2003 has resulted in the continuity of the instant application to Non-Provisional Application No. 60/227,714 being broken. As such, the instant application is not entitled to the filing date of the '714 or '846 application.

The earliest effective U.S. filing date of the instant application has been determined to be 2/17/2004.

Information Disclosure Statement

Acknowledgment is made of the information disclosure statement (IDS) submitted on 2/17/2004. The examiner is considering the information disclosure statement to the extent that each reference cited therein is a proper citation. Please see attached Form 1449.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claim 6 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not reasonably be appraised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Meyskens *et al.* (US 2002/0137797; published 9/26/2002).

As discussed *supra*, the instant application is not entitled to the benefit and priority of either U.S. Provisional Application No. 60/227,714, filed August 24, 2000 or U.S. Non-Provisional Application No. 09/938,846, filed 8/24/2001. As such, Meyskens *et al.* is applicable as prior art under 35 U.S.C. § 102(b) because it was published more than one year before the earliest effective U.S. filing date of the instant application.

Meyskens *et al.* is the U.S. Patent Application Publication of application no. 09/938,846. The document teaches the instantly claimed methods verbatim (see Claims 1-20 at page 14).

Claims 1 and 3-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bey *et al.* (U.S. Patent No. 4,330,559; Issued May 18, 1982) (prior art of record).

The instant claims recite a method of decreasing spermine and/or spermidine levels in a human prostate cell by administering α-difluoromethylornithine (α-DMFO).

Bey *et al.* disclose a method of treating benign prostatic hypertrophy comprising administration of α-DMFO (col. 1, lines 22-25 and col. 2, lines 36-40). Benign prostatic hypertrophy as used in Bey *et al.* means any enlargement of the prostate, including that due to hyperplasia (col. 1, lines 17-21). α-DMFO is taught to irreversibly inhibit ornithine decarboxylase (ODC), the enzyme which catalyzes the decarboxylation of ornithine to putrescine (col. 2, lines 48-51). This decarboxylation step is the first step in the biosynthesis of the polyamines spermidine and spermine (*id.*). Since putrescine is a precursor of the polyamines, "it is seen that blockade of the conversion of ornithine to putrescine, such as by inhibition of ODC, can provide a method for regulating the cellular levels of the polyamines" (col. 3, lines 8-12).

The compounds taught in Bey *et al.*, including α-DMFO, can be administered orally (col. 3, line 42) to humans (col. 3, line 66) in amounts ranging from 10 mg/kg to 1 g/kg of body weight per day (col. 3, lines 51-52). The compounds taught in Bey *et al.* "can be used as their racemic mixtures or as individual enatiomers" (col. 2, lines 41-47). Further, it is taught that administration occurs from the "onset of hypertrophy of the prostate to *regression of the disease*" (col. 3, lines 61-63). Thus, the methods taught in Bey *et al.* inherently read on administration of α-DMFO to a human for <u>any</u> amount of time necessary to regress the disease.

With regard to the instantly claimed doses, it is noted that the doses taught in Bey *et al.* read on the instantly claimed doses. For example, instant claim 14 recites administration of about "0.1 to 2.0 gm/m^2/day". The average human male weighs approximately 77 kg and has a body surface area of 1.95 m^2. Thus, the doses taught in Bey *et al.* fall within the instantly claimed ranges.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 2 and 5-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Weis *et al.* (WO 98/25603).

Weis *et al.* disclose the use of single enantiomers of DMFO to prevent/treat cancers and their metastases, including prostate cancer, in humans (page 13, lines 15-32 and page 14, line 6). Administration is by a variety of dosage forms, including oral (page 17, lines 24 and 29, for example). The preferred dosage range of 0.5 to 3.0 g/m^2/day (page 23, last paragraph) is the same as that used by the applicant (compare with instant claims 14-19). Treatment is specified for a period of 1 to 365 days (page 14, line 22), but may be continued as long as necessary (page 14, line 26). When used for prevention, administration may be chronic, *i.e.* indefinite for as long as required (page 23, line 20). The prior art treatment results in a reduction of polyamine levels,

including putrescine, spermidine and spermine (page 1, lines 27-30 and Tables 1-3 at pages 40-42). Levels can be reduced effectively to zero, *i.e.* to an undetectable level (page 1, line 28).

The prior art is not anticipatory under 35 U.S.C. § 102 because prostate cancer must be selected from a relatively large list of diverse alternative cancers provided at page 13, lines 15-21 of the prior art. This is reinforced by the fact that prostate cancer is not exemplified in the form of a discrete preferred embodiment, such as a working example (the prior art working examples exemplify only melanoma and leukemia at pages 37-38). However, it would most certainly have been obvious to have treated prostate cancer, motivated by the prior arts specific disclosure that species and its clear invitation to select alternatives.

Thus, the prior art fairly suggests the instantly claimed methods. Moreover, the prior art clearly suggests optimizing therapeutic parameters, *e.g.* varying the course and duration of administration, as well as dosage, depending on the particular patients being treated and the severity of their cancers (page 23, lines 15-20). Accordingly, the various instant recitations of particular durations (claims 11-14) and dosages (claims 14-19) would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-5 and 7-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Messing *et al.* (prior art of record) in view of Meyskens *et al.* (prior art of record) and Mohan *et al.* (prior art of record).

The instant claims recite a method of decreasing spermine and/or spermidine levels in a human prostate cell by administering α-difluoromethylornithine (α-DMFO).

Messing *et al.* disclose the administration of 0.5 g/m^2 of α-DMFO once daily for two weeks to human patients having prostate cancer (page 1416). Said administration results in statistically significantly lower levels of putrescine, the precursor to spermidine and spermine (*id.*). Spermidine and spermine concentrations were similar in treated and control groups. Difluoromethylornithine is a known inhibitor of ornithine decarboxylase activity and reduces putrescine and occasionally spermidine levels. The authors state that "[I]t is uncertain whether a longer duration of administration of difluoromethylornithine would have depleted the other polyamines [spermidine and spermine] from prostatic tissue" (page 1416, right column).

Meyskens *et al.* is provided to demonstrate that DMFO was known in the art to suppress all prostate polyamine pools, including the spermine pool when administered to men scheduled for surgical interventions to treat some form of prostate hyperplasia or neoplasia (page 946, right column).

Mohan *et al.* disclose that ornithine decarboxylase is the first and rate-limiting step in the biosynthesis of polyamines (putrescine, spermidine, and spermine) in mammalian cells (page 143, right column). Further, it is disclosed that in humans, among all tissues, the highest concentration of polyamines and polyamine synthetic enzymes, especially ornithine decarboxylase, occurs in the prostate (page 144, left column). Ornithine decarboxylase activity is disclosed to be significantly increased in prostate cancer tissue (Fig. 1).

In the absence of a showing of unexpected results commensurate in scope with the claims, the instantly claimed method of decreasing spermine and spermidine levels in human prostate and hyperplasia cells by administering α-DMFO would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Mohan *et al.* disclose that

ornithine decarboxylase activity is increased in prostate cancer tissue. Meyskens *et al.* disclose that all prostate polyamine pools, including the spermine pool, are suppressed is men treated with DMFO. Finally, Messing *et al.* disclose administration of α-DMFO in the same amounts and to the same patient population as the instantly claimed methods. The direct precursor (putrescine) to the polyamines spermine and spermidine was lowered by α-DMFO treatment. As such, it would have been obvious to administer α-DMFO for longer periods of time to allow for a decrease in polyamine levels to occur. This is especially true given that Meyskens *et al.* disclose that all prostate polyamine pools, including the spermine pool, are suppressed is men treated with DMFO.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
AU 1614

October 11, 2006

Ardin H. Marschel 10/14/06
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SUPERVISORY PATENT EXAMINER